**Advanced Computational Methods in Dose Modeling: Application of Computational Biophysical Transport, Computational Chemistry, and Computational Biology**

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Computational toxicology (CompTox) leverages the significant gains in computing power and computational techniques (e.g., numerical approaches, structure-activity relationships, bioinformatics) realized over the last few years, thereby reducing costs and increasing efficiency in hazard evaluations, screening assessments, and multi-chemical risk assessments. In this work, we draw upon innovations in CompTox to reduce uncertainties in route-to-route, species-to-species, and other dose extrapolations that are commonly performed in multi-chemical risk assessments. Biophysical transport theory applies computational fluid dynamics and mass transport methodologies to reduce uncertainties in inhalation dosimetry of aerosols and vapors. These computational approaches strengthen the linkage between exposure and absorption of pollutants. Through development of structure-activity relationships, computational chemistry can reduce uncertainties in dose modeling by reducing bias and imprecision in parameter estimation (e.g., metabolic rate constants, enzyme inhibition constants). Computational biology applies "omics" (e.g., genomics, proteomics, and metabonomics) within a dose-modeling framework to better account for differences in chemical disposition within populations, across species, and over a range of exposure regimes. Information on interindividual differences (i.e., gene polymorphisms), as well as species-specific parameters and/or multiple exposure scenarios, may be directly incorporated within a physiologically based pharmacokinetic model to evaluate their effect on a toxic metabolite. (Although this work was reviewed by EPA and approved for publication, it may not necessarily reflect official Agency Policy.)